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miRNAs in coronary artery disease pathophysiology: mechanisms and diagnostic perspectives

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Abstract

Coronary artery disease (CAD) remains a leading cause of morbidity and mortality worldwide, largely driven by atherosclerotic processes within the coronary arteries. Non-coding RNAs (ncRNAs), a diverse group that includes microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), have emerged as crucial regulators of cardiovascular biology. Among these, miRNAs are particularly well-studied for their ability to fine-tune gene expression and modulate key cellular events, such as inflammation, endothelial dysfunction, vascular remodeling, and apoptosis—all of which are central to CAD pathogenesis. This narrative review provides a comprehensive synthesis of the current evidence on the roles of miRNAs in CAD, emphasizing their mechanistic contributions and clinical potential as candidates for diagnosis and prognosis. The review also addresses the diagnostic performance of specific miRNAs, discusses their utility in distinguishing between stable CAD and acute coronary syndromes, and critically appraises methodological challenges such as study heterogeneity and lack of standardization. While miRNAs represent a promising frontier for improved risk stratification and targeted therapy in CAD, further research is needed to clarify their complex regulatory networks and translate these findings into clinical practice. The integration of miRNA research with broader ncRNA studies may ultimately enhance our understanding of CAD and foster the development of novel diagnostic and therapeutic strategies.

Keywords: *coronary artery disease, non-coding RNAs, microRNAs, biomarkers, pathophysiology, diagnosis, prognosis*

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1. Introduction

Coronary artery disease (CAD) represents a predominant contributor to global morbidity and mortality, characterized by the atherosclerotic constriction of coronary arteries, which can precipitate myocardial ischemia and infarction [1]. Recent advancements in molecular biology accentuate the crucial role of microRNAs (miRNAs), which are small non-coding RNA molecules, in modulating gene expression and influencing various pathophysiological mechanisms associated with CAD [2]. These molecules are implicated in critical processes such as endothelial dysfunction, inflammation, and vascular remodeling, all of which are fundamental to the onset and progression of atherosclerosis [3].

The exploration of miRNAs in the context of CAD holds significant importance, particularly concerning their potential utility as biomarkers for early detection and prognosis [4]. Existing diagnostic modalities for CAD, while generally effective, frequently suffer from limitations in specificity and sensitivity, which can result in delayed intervention and an elevated risk of adverse clinical outcomes [5]. The identification of circulating miRNAs as biomarkers presents a promising pathway for enhancing early diagnosis and risk stratification in CAD patients [6]. Research has demonstrated that certain miRNAs can correlate with the severity of coronary artery lesions and may even serve as predictors of future cardiovascular events [7]. Thus, a thorough perception of miRNA involvement in CAD could markedly improve clinical practices.

Despite the expanding literature on miRNAs within cardiovascular pathology, significant gaps remain in our comprehension of their precise mechanisms of action in CAD. Although numerous investigations have identified dysregulated expression profiles of miRNAs in individuals with CAD, the functional implications of these alterations often remain ambiguous [8]. Moreover, the interactions between different miRNAs and their combined impact on disease progression remain underexplored. This review aims to fill knowledge gaps regarding miRNA's role in CAD and identifies areas for future research. It thoroughly examines both established and emerging miRNAs related to CAD, emphasizing their roles as disease modulators and potential biomarkers for clinical use. The study intends to investigate the effect of miRNAs in CAD progression, assess their diagnostic and prognostic value, and suggest directions for new therapeutic research.

2. Methodology

This narrative review was conducted to synthesize and critically appraise the current evidence on the role of miRNAs in CAD. To ensure a comprehensive and balanced overview, we systematically searched multiple electronic databases, including PubMed, Scopus, and Web of Science, for articles published in English from January 2010 to January 2025. The primary search terms

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included combinations of "microRNA", "miRNA", "coronary artery disease", "atherosclerosis", "biomarker", and "pathophysiology". Additional relevant articles were identified by screening the reference lists of key reviews and original research papers.

Inclusion criteria comprised original studies, systematic reviews, and meta-analyses that investigated the expression, function, or clinical utility of miRNAs in human CAD or relevant animal models. We excluded case reports, editorials, conference abstracts, and studies lacking primary data on miRNA involvement in CAD. Priority was given to studies with clearly defined patient populations, robust experimental designs, and validated miRNA measurement techniques.

Two authors independently screened the titles and abstracts for relevance, followed by a full-text assessment. Discrepancies were resolved through discussion or consultation with a third reviewer. The quality of included studies was appraised informally, considering factors such as sample size, methodological rigor, and consistency with established guidelines. Given the narrative nature of this review, we did not perform a formal risk-of-bias assessment or quantitative synthesis.

2.1. Laboratory methods for detection of ncRNAs

Several advanced molecular techniques are used to detect and quantify ncRNAs, including miRNAs. Common methods include quantitative real-time PCR (qRT-PCR), the gold standard for the sensitive and specific quantification of known ncRNAs, allowing for the detection of low-abundance transcripts and suitable for biomarker studies [9]; RNA immunoprecipitation (RIP), which identifies RNAs associated with specific RNA-binding proteins, elucidating ncRNA regulatory complexes [10]; crosslinking and immunoprecipitation (CLIP) and its variants (e.g., HITS-CLIP, PAR-CLIP), providing high-resolution mapping of RNA–protein interactions to pinpoint ncRNA binding sites [11]; chromatin immunoprecipitation (ChIP), adaptable for investigating ncRNA roles in chromatin remodeling and gene regulation [12]; and next-generation sequencing (NGS), such as small RNA-seq, enabling comprehensive ncRNA expression profiling, novel ncRNA discovery, and analysis of isoforms/variants [13]. These techniques have significantly advanced our understanding of ncRNAs and their biomarker potential. Method selection depends on the research question, ncRNA type, and available sample.

3. ncRNA classes

More than 85% of the human genome is transcribed into non-coding RNAs (ncRNAs), while only about 2% of RNA transcripts encode known proteins [14]. Far from being residual or non-functional genomic "waste", ncRNAs are now recognized as indispensable functional molecules that play critical regulatory roles in gene expression, cellular signaling, and the maintenance of physiological homeostasis [15, 16]. Based on their size, structure, and function, ncRNAs are broadly classified into several major categories, each with unique characteristics and biological roles [16]. **Table 1** provides an overview of the principal classes of ncRNAs, their typical nucleotide lengths, and their general functions, with particular emphasis on their relevance to cardiovascular disease, including CAD.

Table 1 • Major classes of ncRNAs, their typical lengths, and general functions/relevance to CAD.

ncRNA class	Typical length (nucleotides)	General function/relevance to CAD
miRNAs	~20–24	Post-transcriptional gene regulation; modulate inflammation, endothelial function, and cardiac remodeling in CAD [17].
lncRNAs	>200	Regulate chromatin, transcription, and post-transcriptional processes; involved in vascular remodeling and atherogenesis [18].
piRNAs	24–31	Silence transposable elements, mainly in germ cells; emerging roles in vascular biology [19].
siRNAs	~21–23	Mediate RNA interference and gene silencing; used experimentally in cardiovascular research [20].
circRNAs	Variable (hundreds to thousands)	Form covalently closed loops; act as miRNA sponges, regulate gene expression, involved in heart development and disease [21].
Vesicle-associated RNAs (e.g., exosomal RNAs)	Variable	Packaged within extracellular vesicles; facilitate intercellular communication and may serve as circulating biomarkers for CAD [22].

lncRNAs = Long non-coding RNAs, piRNAs = Piwi-interacting RNAs, siRNAs = Small interfering RNAs, circRNAs = Circular RNAs, CAD = Coronary artery disease.

4. Functional clusters of miRNAs in coronary artery disease pathogenesis

miRNAs are small, ncRNAs playing a fundamental role in the regulation of gene expression at the post-transcriptional level [23] by binding to complementary sequences on target messenger RNAs (mRNAs), which results in either mRNA degradation or the inhibition of translation [24]. Dysregulation of these ncRNAs significantly contributes to the pathophysiology of CAD, particularly across various stages of atherogenesis, such as inflammation, endothelial dysfunction, and smooth muscle cell (SMC) proliferation and apoptosis within the coronary arteries (**Figure 1**) [25]. While some mechanistic insights are derived from studies in large vessels such as the aorta or carotid arteries, similar processes are implicated in coronary artery SMCs and the progression of CAD [26].

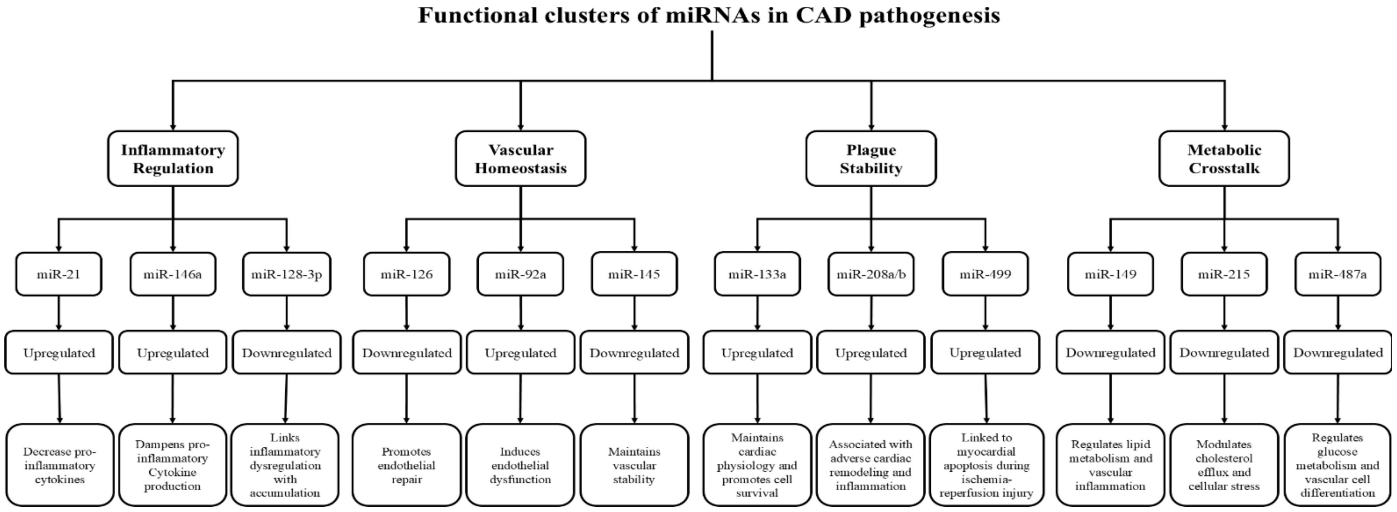

Figure 1 • Four miRNA groups involved in CAD: inflammation (miR-21, miR-146a, miR-128-3p), vascular health (miR-126, miR-145, miR-92a), plaque stability (miR-133a, miR-208a/b, miR-499), and metabolic crosstalk (miR-149, miR-215, miR-487a), highlighting their dysregulation and roles in disease processes.

Recent studies have shown that ncRNAs, including miRNAs, are often packaged within extracellular vesicles such as exosomes, which facilitate their stable transport through circulation and enable their delivery to the recipient (i.e., target) cells [27]. This exosome-mediated transfer is increasingly recognized as a key mechanism for intercellular communication in cardiovascular disease, including CAD [28].

miRNAs can also be expressed as multiple isoforms, known as "isomiRs", which may have distinct regulatory roles [29]. For instance, miR-133 exists in three isoforms—miR-133a1, miR-133a2, and miR-133b—each encoded by different genomic loci but sharing highly similar sequences and overlapping functions in cardiac physiology and disease [30]. These isoforms underscore the complexity of miRNA-mediated regulation in cardiovascular disease, as subtle sequence differences may influence target specificity and functional outcomes [31].

4.1. Inflammatory regulation

Inflammation is a central driver of atherosclerosis and CAD, and several miRNAs have been shown to play pivotal roles in modulating inflammatory responses within the vascular wall [32]. Among these, miR-21, miR-146a, and miR-128-3p regulate key aspects of immune cell activation, cytokine signaling, and plaque progression.

miR-21 is consistently upregulated in CAD and acts as a regulator of inflammation by targeting genes involved in cytokine production and immune cell adhesion [33]. It suppresses the expression of pro-inflammatory cytokines and adhesion molecules, thereby reducing immune cell infiltration into atherosclerotic plaques and ameliorating the inflammatory milieu. However, the persistent overexpression of miR-21 can also promote adverse cardiac remodeling [34].

The expression of miR-146a has been associated with the modulation of inflammatory responses during the formation of atherosclerotic plaques [35]. This miRNA serves as a negative feedback regulator of inflammation, particularly in macrophages. By targeting components of the NF-κB signaling pathway, miR-146a dampens the production of pro-inflammatory cytokines and modulates macrophage activation, thus influencing both the formation and stability of atherosclerotic plaques. Its upregulation in CAD patients is associated with ongoing vascular inflammation and may serve as a marker for inflammation-driven disease progression [36, 37].

miR-128-3p is typically downregulated in CAD and atherosclerosis. Reduced expression of miR-128-3p leads to increased cholesterol accumulation in macrophages, promoting foam cell formation—a hallmark of early atherogenesis [38]. This miRNA thereby links inflammatory dysregulation with lipid-driven plaque development.

4.2. Endothelial and vascular homeostasis

Endothelial integrity and vascular homeostasis are essential for preventing the initiation and progression of CAD. Several miRNAs, notably miR-126, miR-92a, and miR-145, regulate endothelial function, smooth muscle cell (SMC) behavior, and vascular remodeling. Dysregulation of theses miRNAs disrupts vascular homeostasis, accelerates atherosclerotic changes in the coronary arteries, and increases the risk of adverse cardiovascular events [39, 40].

miR-126 is a key regulator of vascular homeostasis. It promotes endothelial cell proliferation, migration, and repair by targeting inhibitors of the VEGF signaling pathway [41]. Downregulation of miR-126 in CAD is associated with impaired endothelial function, reduced nitric oxide bioavailability, and heightened vascular inflammation, all of which contribute to atherogenesis and plaque progression [42].

miR-92a is a critical modulator of endothelial dysfunction. Its upregulation in CAD leads to decreased endothelial regeneration and increased vascular inflammation by suppressing pro-angiogenic factors and enhancing oxidative stress [43]. Elevated miR-92a levels are linked to impaired endothelial repair and a greater propensity for atherosclerotic lesion development [44].

miR-145 is predominantly expressed in vascular SMCs, and it plays a pivotal role in maintaining vascular stability. It promotes SMC differentiation and the contractile phenotype while inhibiting abnormal proliferation and migration [45, 46]. The downregulation of miR-145 in CAD is associated with SMC dedifferentiation, increased neointimal formation, and plaque instability, thereby contributing to adverse vascular remodeling [47].

4.3. Plaque stability and remodeling

The stability of atherosclerotic plaques and vascular remodeling are pivotal determinants of clinical outcomes in CAD. The dysregulation of miRNAs such as miR-133a, miR-208a/b, and miR-499 directly impacts these processes, influencing plaque vulnerability and myocardial repair mechanisms [48, 49].

miR-133a is critical for maintaining cardiac physiology and promoting cell survival. It modulates extracellular matrix (ECM) composition by targeting collagenases and metalloproteinases (e.g., MMP-9), thereby influencing plaque stability [50]. Elevated circulating miR-133a levels correlate with acute coronary syndrome (ACS), where it serves as a biomarker for distinguishing unstable plaques from stable CAD [51].

miR-208a/b, cardiac-enriched miRNAs, are strongly associated with adverse cardiac remodeling and inflammation. miR-208a/b promotes fibroblast activation and collagen deposition, contributing to fibrotic cap formation in plaques [52]. However, excessive upregulation destabilizes plaques by enhancing SMC apoptosis and inflammatory cytokine release (e.g., IL-6), exacerbating ischemic injury [52].

miR-499 via regulating mitochondrial permeability and caspase-3 activation promotes myocardial apoptosis during ischemia–reperfusion injury [53]. In coronary plaques, its overexpression correlates with necrotic core expansion and thinning of the fibrous cap, hallmarks of rupture-prone lesions. Paradoxically, miR-499 also facilitates reparative angiogenesis in peri-infarct zones, highlighting its dual role in remodeling [54].

4.4. Metabolic crosstalk

Metabolic dysregulation, particularly involving lipid and glucose metabolism, is a key driver of CAD progression and heterogeneity [55]. A subset of miRNAs—including miR-149, miR-215, and miR-487a—form a functional cluster that modulates metabolic pathways, influencing both atherogenesis and plaque stability.

The downregulation of miR-149 has been observed in CAD, especially in patients with acute coronary syndrome [56]. miR-149 regulates genes involved in lipid metabolism and vascular inflammation, and its low expression is associated with increased endothelial dysfunction and heightened risk for plaque destabilization [57]. Circulating miR-149 has demonstrated high sensitivity and specificity in distinguishing stable CAD from ACS, highlighting its diagnostic value [57].

miR-215, typically downregulated in stable CAD, is thought to exert a protective effect against disease progression [58]. It modulates genes involved in cholesterol efflux and cellular stress responses, potentially limiting lipid accumulation within the arterial wall [59]. Lower miR-215 levels may reflect impaired metabolic adaptation and increased vulnerability to atherosclerotic advancement [60].

miR-487a, also downregulated in stable CAD, is implicated in the regulation of glucose metabolism and vascular cell differentiation [61]. Its decreased expression may contribute to adverse metabolic remodeling and facilitate the transition from stable to unstable plaque phenotypes. miR-487a's role in metabolic crosstalk suggests it may be a marker for disease progression risk [62].

5. miRNA dysregulation in coronary artery disease

Numerous studies have identified several miRNAs that are consistently dysregulated in patients with CAD compared to healthy controls, significantly contributing to the disease's pathophysiology [63, 64] (**Table 2**).

MiR-21 has been associated with promoting cell survival and proliferation; however, its overexpression often correlates with adverse cardiac remodeling and unfavorable outcomes in CAD patients [65].

In acute coronary syndrome (ACS), specific miRNAs, including miR-499 and miR-133a/b, have been recognized as potential biomarkers for distinguishing ACS from stable CAD [66]. Notably, miR-133a appears in the bloodstream within hours of ischemic injury, much earlier than traditional cardiac biomarkers such as cardiac troponins, highlighting its potential value for the early diagnosis of myocardial damage [67].

In contrast, certain miRNAs, such as miR-215 and miR-487a, have exhibited downregulation in stable CAD, suggesting a protective role against disease advancement [68].

Therefore, circulating levels of some specific miRNAs can act as reliable biomarkers for both the diagnosis and prognosis of CAD. A systematic review has indicated that circulating levels of miR-133a and miR-149 can effectively differentiate between stable CAD and ACS with high sensitivity and specificity [69]. The area under the curve (AUC) values for these biomarkers often exceed 0.9, reflecting excellent diagnostic performance. These findings highlight the potential utility of circulating miRNAs in clinical practice for the early detection and monitoring of CAD [70].

The mechanisms causing miRNA dysregulation are under active investigation. Oxidative stress, inflammation, and lipid accumulation, all factors in CAD pathogenesis, influence miRNA expression [71]. For instance, reduced levels of miR-128-3p have been linked to increased cholesterol accumulation in macrophages, leading to foam cell formation, a critical event in the development of atherosclerosis and the progression of CAD. Although most evidence for miR-128-3p's role comes from studies in non-coronary vascular beds, similar mechanisms are believed to contribute to coronary artery atherosclerosis and CAD progression [72, 73].

Table 2 • Dysregulation of specific miRNAs in CAD.

MicroRNA	Expression in CAD	Role in CAD pathophysiology	Study type	Population (N, demographics)	Diagnostic metrics (AUC, Sens, Spec)
miR-1	Upregulated	Involved in cardiac growth and apoptosis	Clinical/ Preclinical	Human studies/Animal models	To be determined [74, 75]
miR-133a	Upregulated	Critical for cardiac physiology; promotes cell survival	Clinical	Human	High sensitivity for differentiating stable CAD from ACS [67]
miR-208a/b	Upregulated	Cardiac remodeling and inflammation	Clinical/ Preclinical	Human	Associated with myocardial injury [52]
miR-499	Upregulated	Related to myocardial injury, inflammation	Clinical	Human	Potential biomarker for ACS vs. stable CAD [76]
miR-21	Upregulated	Promotes cell survival, inflammatory regulation	Clinical	Human	Indicator of adverse remodeling and outcomes [65]
miR-146a	Upregulated	Regulates inflammation in plaques	Clinical	Human	Marker for inflammation-related CAD progression [35]
miR-126	Dysregulated (often reduced)	Endothelial function, angiogenesis	Clinical/ Preclinical	Human	Biomarker for endothelial health [41]
miR-145	Promotes SMC differentiation	Stabilizes plaques, reduces proliferation	Clinical	Human	Potential role in plaque stability [45]
miR-128-3p	Downregulated	Cholesterol metabolism, foam cell formation	Clinical	Human	Reflects atherosclerosis development risk [38]
miR-487a	Downregulated	Protective in stable CAD	Clinical	Human	Indicates disease progression risk [61]
miR-215	Downregulated	Possible protective role	Clinical	Human	Diagnostic in stratification [60]
miR-208b	Upregulated	Associated with adverse outcomes	Clinical	Human	Prognostic biomarker [77]
miR-197	Upregulated	Related to prognosis	Clinical	Human	Prognostic relevance [78]
miR-223	Error in listing; generally linked to long-term outcomes	Long-term mortality and risk assessment	Clinical	Human	To be determined [79]
miR-378	Downregulated	Disease severity differentiation	Clinical	Human	Potential diagnostic tool [63]
miR-210-3p	Downregulated	Vascular function, lipid metabolism	Clinical	Human	Diagnostic/ prognostic marker [80]
miR-195-5p	Emerging diagnostic potential	Disease assessment and hypertension	Clinical	Specific populations	To be determined [81]
miR-149	Downregulated	Vascular inflammation and plaque stability	Clinical	Human	Differentiates stable CAD from ACS [82]
miR-92a	Upregulated	Impairs endothelial function; promotes atherosclerosis	Preclinical/ Clinical	Human/Animal models	To be determined [43]
miR-206	Dysregulated	Modulates angiogenesis via VEGF signaling	Preclinical	Animal models	To be determined [83]

Population (N, demographics) = Number of participants and their demographic details (age, sex, health status), Diagnostic metrics (AUC, Sens, Spec) = Performance measures for miRNAs as diagnostic tools, AUC = Area Under the Receiver Operating Characteristic Curve—measures overall diagnostic accuracy, Sens = Sensitivity—ability to correctly identify true positives, Spec = Specificity—ability to correctly identify true negatives.

5.1. miRNA networks in coronary artery disease comorbidities

The pathophysiology of CAD is frequently complicated by common comorbidities such as diabetes mellitus and hypertension, both of which further modulate the expression and function of circulating and tissue-specific miRNAs [84]. In diabetic CAD, hyperglycemia and insulin resistance amplify endothelial dysfunction and vascular inflammation, leading to distinct miRNA expression profiles compared to non-diabetic CAD [85]. For example, miR-126, a key regulator of endothelial homeostasis, is more profoundly downregulated in CAD patients with diabetes, exacerbating vascular injury and impairing reparative capacity [86]. Similarly, miR-146a, which modulates inflammatory signaling, shows altered regulation in the context of chronic hyperglycemia, potentially contributing to persistent vascular inflammation and accelerated atherosclerosis [35].

Hypertension, another major CAD comorbidity, is associated with unique miRNA signatures that reflect increased vascular stiffness and remodeling [87]. Notably, miR-145, which promotes smooth muscle cell differentiation and vascular stability, is often further suppressed in hypertensive CAD patients, contributing to adverse vascular remodeling and plaque instability [88]. These comorbidity-specific miRNA changes can influence both the clinical presentation of CAD and the utility of miRNA-based biomarkers for risk stratification.

A comparative overview of key miRNAs differentially expressed in CAD, CAD with diabetes, and CAD with hypertension is provided in **Table 3**.

6. miRNAs as potential biomarkers in coronary artery disease

Despite several technical challenges, the distinctive properties of miRNAs, including their stability in circulation, tissue specificity, and capacity to reflect pathological changes within the cardiovascular system, introduce them as potential biomarkers for both the diagnosis and prognosis of CAD [89–91]. Additionally, utilizing miRNA panels may help address the limitations associated with single biomarker evaluations, such as variability in sensitivity and specificity across different populations.

miRNAs can be easily detected in bodily fluids such as serum and plasma and reflect both the physiological and pathological states of tissues [92]. The detection and quantification of miRNAs in biological samples rely on several advanced molecular techniques [93]. Among the most commonly used methods are real-time quantitative polymerase chain reaction (qRT-PCR) [9], RNA immunoprecipitation (RIP) [10], crosslinking and immunoprecipitation (CLIP) and its variants (e.g., HITS-CLIP, PAR-CLIP) [11], chromatin immunoprecipitation (ChIP) [12], and next-generation sequencing (NGS) [13]. The choice of method depends on the specific research question, the type of ncRNA under investigation, and the available sample material.

Among the most extensively studied miRNAs in relation to CAD is miR-133a. Evidence suggests that levels of miR-133a are significantly elevated in patients experiencing unstable angina and acute myocardial infarction, highlighting its potential as an early biomarker for these conditions [94]. In comparative analyses, miR-133a has demonstrated an area under the curve (AUC) value of 0.918, better than traditional biomarkers such as cardiac troponin I (cTnI) in differentiating CAD from non-CAD individuals [95]. Furthermore, incorporating miR-133a into clinical data and cTnI measurements has been shown to enhance diagnostic accuracy, underscoring its role as a robust biomarker for CAD assessment [96].

In addition to miR-133a, other miRNAs, including miR-1, miR-208a, and miR-499, have also been identified as potential biomarkers for CAD. For example, elevated levels of miR-208a have been detected shortly after myocardial infarction, occurring prior to traditional markers such as cTnI and creatine kinase–MB (CK-MB) [97]. This early release indicates that miRNAs may provide timely insights regarding myocardial injury, thereby improving patient management in emergency situations.

Also, miR-499 is capable of distinguishing between acute myocardial infarction and other forms of cardiac stress, with studies demonstrating its sensitivity and specificity comparable to traditional biomarkers like cardiac troponins [98].

Moreover, recent studies have demonstrated that combinations of circulating miRNAs can enhance diagnostic performance; for instance, the combination of miR-1 and miR-126 with miR-133a has exhibited a high predictive capability for distinguishing between stable and unstable CAD [99, 100] (**Table 4**).

Table 3 • Differential miRNA dysregulation in CAD with and without diabetes/hypertension.

MicroRNA	CAD alone	CAD + diabetes mellitus	CAD + hypertension	Pathophysiological/clinical implication
miR-126	Downregulated	Further downregulated	Downregulated	Endothelial dysfunction, impaired repair [86]
miR-146a	Upregulated	Altered/attenuated response	Upregulated	Inflammatory modulation, persistent vascular inflammation [35]
miR-145	Downregulated	Downregulated	Further downregulated	SMC dedifferentiation, vascular remodeling, plaque instability [47]
miR-133a	Upregulated	Upregulated	Upregulated	Myocardial injury, potential biomarker [67]
miR-21	Upregulated	Upregulated	Upregulated	Fibrosis, adverse remodeling [65]
miR-499	Upregulated	Upregulated	Upregulated	Myocardial apoptosis, ACS marker [54]
miR-215	Downregulated	Downregulated	Downregulated	Protective effect, diagnostic potential [60]

Table 4 • The roles of specific miRNAs as potential biomarkers in CAD.

MicroRNA(s)	Study type	Sample size and population	Measurement technique and normalization	Diagnostic metrics (sensitivity, specificity, AUC)	Main conclusions and limitations
miR-133a	Case–control	150 CAD patients, age 45–70, diverse ethnicity	qRT-PCR, normalization to U6 snRNA	Sensitivity: 85%; specificity: 88%; AUC: 0.918 (95% CI: 0.89–0.94)	High diagnostic accuracy; potential batch effects [94].
miR-208a	Cohort	120 post-MI patients, mixed gender	TaqMan qRT-PCR, cel-miR-39 spike-in	Sensitivity: 82%; specificity: 80%; AUC: 0.910	Early marker for myocardial injury; external validation needed [101].
miR-1	Case–control	100 stable, 100 unstable CAD; age 50–75	qRT-PCR, normalization to miR-16	Sensitivity: 78%; specificity: 75%; AUC: 0.85	Good predictive value; limited longitudinal data [102].
miR-499	Cross-sectional	75 ACS, 75 stable CAD	Digital PCR, normalization to U6	Sensitivity: 80%; specificity: 82%; AUC: 0.88	Useful in acute phase; reproducibility issues reported [103].
miR-21	Prospective	200 CAD patients; diverse demographic	qRT-PCR, normalized to GAPDH	Sensitivity: 70%; specificity: 65%; AUC: 0.75	Prognostic relevance; batch and platform variability affect results [104].
miR-128-3p	Observational	90 CAD patients, 90 controls	NGS plus qRT-PCR validation	Sensitivity: 76%; specificity: 78%; AUC: 0.80	Non-invasive marker; further validation needed [38].
miR-195-5p	Regional cohort	100 Indian CAD patients	qRT-PCR, normalization to RNU48	Sensitivity: 72%; specificity: 70%; AUC: 0.78	Population-specific utility; broader studies required [105].

qRT-PCR = Quantitative Reverse Transcription Polymerase Chain Reaction, U6 snRNA = U6 small nuclear RNA, cel-miR-39 = Caenorhabditis elegans microRNA 39, GAPDH = Glyceraldehyde 3-phosphate dehydrogenase, RNU48 = RNA, U6 small nuclear 48; NGS = Next-Generation Sequencing, AUC = Area Under the Receiver Operating Characteristic (ROC) Curve, CI = Confidence Interval.

The potential of circulating miRNAs extends beyond diagnostic applications (**Table 5**); they also serve as prognostic markers. Research indicates that specific miRNA expression profiles correlate with disease severity and outcomes in CAD patients [25, 106]. For instance, the downregulation of miR-21 has been linked to an increased risk of adverse cardiovascular events in patients with significant coronary artery stenosis [107, 108]. Conversely, increased levels of specific miRNAs, such as miR-21, miR-146a, miR-126, miR-133a, miR-208a/b, miR-499, and miR-197 may indicate a greater risk of plaque instability and cardiovascular events [109, 110].

Elevated levels of miR-133a have been associated with increased mortality in CAD patients, with meta-analyses reporting a pooled hazard ratio (HR) of 2.35 for individuals exhibiting high expression levels linked to poor outcomes [94, 111].

Table 5 • Prognostic Value miRNAs in CAD.

MicroRNA	Prognostic significance	Associated clinical events	Hazard ratio (HR)
miR-133a	High expression is linked to increased mortality in CAD patients.	Adverse clinical events, including mortality and major adverse cardiac events (MACEs).	HR of 2.35 (95% CI: 1.56–3.55) [94]
miR-208b	Elevated levels correlate with poor outcomes in CAD populations.	Increased mortality and MACEs.	Not specified but a significant association noted [77]
miR-126	High expression is associated with adverse clinical outcomes.	Increased mortality and MACEs in CAD patients.	Not specified but a significant association noted [112]
miR-197	Linked to poor prognosis in CAD cases.	Increased mortality and MACEs observed.	Not specified but a significant association noted [78]
miR-21	Part of multi-miRNA panels, improving prognostic accuracy.	Correlates with cardiovascular outcomes and risk stratification.	Not specified but promising prognostic value indicated [104]
miR-499	Associated with enhanced prediction of cardiovascular outcomes when combined with other miRNAs.	Increased mortality and MACEs in CAD patients.	Not specified but a significant association noted [113]
miR-223	Reduced levels are associated with overall mortality, indicating potential use in risk assessment.	Adverse cardiovascular events and mortality trends noted.	Not specified but a robust association indicated in studies [114]

HR (Hazard Ratio): A measure used in survival analysis to compare the risk of an event (e.g., death, MACE) occurring in one group relative to another over time. An HR > 1 indicates higher risk, while HR < 1 indicates lower risk. CI = Confidence Interval, MACE = Major Adverse Cardiac Events.

6.1. Limitations of miRNAs as biomarkers in diagnosis of coronary artery disease

Despite the promising role of miRNAs as biomarkers for CAD, several challenges persist regarding the standardization of their clinical application. Variability in measurement techniques and the need for validation across diverse populations are critical considerations for translating research findings into clinical practice [115].

Also, the strength and reproducibility of circulating miRNA findings in CAD diagnosis are variable [116]. Many studies are limited by small sample sizes, heterogeneous populations, and inconsistent normalization techniques, which can introduce batch effects and confounders. For example, the sensitivity and specificity of miR-133a for distinguishing ACS from stable CAD have ranged from 0.85 to 0.92, with AUCs often exceeding 0.9, but confidence intervals and external validation are frequently lacking [117]. Differences in RNA extraction protocols and the absence of standardized quality controls further complicate cross-study comparisons. Moreover, few studies systematically adjust for comorbidities or demographic factors, such as age, sex, or ethnicity, which may influence miRNA expression [118]. These limitations underscore the need for larger, multicenter studies with rigorous methodological standards and transparent reporting of diagnostic metrics (see **Table 4** for a comparative summary).

7. Emerging frontiers in miRNA research for coronary artery disease

Recent advances in molecular cardiology have revealed new horizons for the use of miRNAs in CAD beyond their traditional roles as biomarkers [119], including exosomal miRNAs as mediators of intercellular communication, combinatorial miRNA panels for enhanced diagnostic accuracy, and innovative therapeutic editing strategies (**Table 5**).

7.1. Exosomal miRNAs: intercellular communication and early biomarkers

Exosomes are small extracellular vesicles that facilitate the transfer of miRNAs between cells, enabling complex intercellular signaling within the cardiovascular system [120]. Circulating exosomal miRNAs are highly stable and reflect the physiological state of their cells of origin. For example, miR-133a packaged in exosomes appears in the bloodstream within hours of ischemic injury—much earlier than conventional cardiac troponins—making it a promising early biomarker for acute coronary events [121]. Exosomal miRNAs such as miR-126 and miR-208a/b have also been implicated in endothelial repair in CAD and myocardial remodeling, respectively, further underscoring their diagnostic and prognostic potential [122].

7.2. Combinatorial miRNA panels: improving diagnostic precision

While individual miRNAs provide valuable information, combining multiple miRNAs into diagnostic panels can significantly improve sensitivity and specificity for CAD. For instance, a panel including both miR-133a and miR-499 has demonstrated superior accuracy in distinguishing acute coronary syndrome from stable CAD, with area under the curve (AUC) values exceeding 0.9 in some studies [123]. Combinatorial approaches can also account for disease heterogeneity and comorbid conditions, such as diabetes or hypertension, by integrating miRNAs that reflect different aspects of CAD pathophysiology [124].

7.3. Therapeutic editing: targeting miRNAs for disease modification

The therapeutic modulation of miRNAs is an active area of research. Strategies such as antagomirs (antisense oligonucleotides) and CRISPR-based editing aiming to regulate miRNA expression [125]—through the application of inhibitors or mimetic agents—have shown promise in preclinical models [126]. These interventions may reverse pathological changes in CAD by restoring normal gene expression patterns. For instance, silencing pro-atherogenic miRNAs or enhancing anti-atherogenic miRNAs could reduce inflammation and promote endothelial repair mechanisms [127]. For example, the systemic administration of antagomirs targeting pro-atherogenic miRNAs has been shown to enhance re-endothelialization and reduce inflammation in injured arteries [128]. CRISPR/Cas-based technologies offer potential for the precise editing of miRNA genes, enabling the long-term modulation of miRNA expression and potentially durable therapeutic effects (**Table 6**) [129].

Table 6 • Emerging miRNA-based strategies for CAD.

Strategy	Principle/example	Advantages	Limitations/challenges	Clinical potential
Exosomal miRNAs	miR-133a, miR-126 in exosomes	Early detection, high stability, reflects tissue of origin	Standardization of isolation, specificity	High (diagnosis, prognosis) [130]
Combinatorial Panels	miR-133a + miR-499, multi-marker signatures	Increased sensitivity/specificity, captures disease heterogeneity	Requires validation, complex analysis	High (diagnosis, risk stratification) [131]
Therapeutic Editing	Antagomirs, CRISPR-based miRNA modulation	Targeted intervention, potential disease modification	Delivery, off-target effects, long-term safety	Moderate to high (therapy) [132]

8. Conclusions

Recent advances in cardiovascular research have illuminated the complex hierarchical roles that miRNAs play in the development and progression of CAD. At the top of this regulatory cascade are upstream inflammatory miRNAs, such as miR-21 and miR-146a, which act as master regulators by initiating and amplifying vascular inflammation through the modulation of cytokine networks and immune cell activity. These initial signals propagate downstream, influencing the function of intermediate miRNAs like miR-126, miR-92a, and miR-145, which are crucial for maintaining endothelial integrity and orchestrating vascular remodeling. Ultimately, this cascade culminates in the activity of downstream effector miRNAs—including miR-133a, miR-208a/b, and miR-499—that are closely associated with myocardial injury, apoptosis, and acute clinical events such as plaque rupture or infarction. This layered organization highlights the intricate crosstalk and feedback mechanisms that miRNAs employ to shape the trajectory of CAD, underscoring their potential as both biomarkers and therapeutic targets.

Despite these promising insights, several significant challenges hinder the clinical translation of miRNA-based diagnostics and therapies. The absence of standardized protocols for measuring miRNA levels in clinical samples leads to inconsistencies across studies, complicating the establishment of reliable diagnostic thresholds. Furthermore, emerging evidence suggests that miRNA expression can vary by sex, age, and ethnicity, necessitating careful consideration of these variables in both research and clinical settings. Delivering miRNA-targeted therapies specifically to diseased coronary tissues while minimizing off-target effects, remains a significant challenge. Ensuring long-term safety and regulatory compliance, particularly with gene-editing technologies, also poses a significant obstacle.

Looking ahead, the field is poised to benefit from network-based approaches that target miRNA clusters rather than individual molecules, as well as the integration of artificial intelligence to identify robust diagnostic signatures. Personalized strategies that account for comorbidities such as diabetes and hypertension, along with continued innovation in therapeutic editing and delivery systems, will be crucial for realizing the full clinical potential of miRNAs in CAD management.

In conclusion, a miRNA-centric model of CAD integrates hierarchical regulatory networks with clinical and translational realities. Addressing current challenges and embracing emerging technologies will be essential for realizing the full potential of miRNAs in the diagnosis, prognosis, and treatment of CAD.

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Conflict of interest

The authors declare that they have no competing interests.

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The data supporting the findings of this publication can be made available upon request.

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